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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.		
10/829,427	04/22/2004	Keisuke Furukawa	252202US0 7267			
22850 7	7590 01/12/2006		EXAMINER			
•	VAK, MCCLELLAND,	WALICKA, MALGORZATA A				
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	,	1652				
				DATE MAILED: 01/12/2006		

Please find below and/or attached an Office communication concerning this application or proceeding.

		Applicat	on No.	Applicant(s)				
Office Action Summary		10/829,4	27	FURUKAWA ET A	AL.			
		Examine	Г	Art Unit				
			ta A. Walicka	1652				
Period fo	The MAILING DATE of this communication or Reply	appears on th	e cover sheet with the c	orrespondence ad	dress			
WHIC - Exter after - If NO - Failu Any r	ORTENED STATUTORY PERIOD FOR RICHEVER IS LONGER, FROM THE MAILIN sions of time may be available under the provisions of 37 CF SIX (6) MONTHS from the mailing date of this communicatio period for reply is specified above, the maximum statutory pre to reply within the set or extended period for reply will, by seply received by the Office later than three months after the red patent term adjustment. See 37 CFR 1.704(b).	G DATE OF TI FR 1.136(a). In no ex n. eriod will apply and v statute, cause the app	HIS COMMUNICATION rent, however, may a reply be time till expire SIX (6) MONTHS from a plication to become ABANDONED	I. sely filed the mailing date of this co (35 U.S.C. § 133).				
Status								
1)🖂	Responsive to communication(s) filed on 2	23 November 2	005.					
· · · —								
3)	Since this application is in condition for allowance except for formal matters, prosecution as to the merits is							
	closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11, 453 O.G. 213.							
Dispositi	on of Claims							
5)□ 6)⊠ 7)□	Claim(s) <u>1-10</u> is/are pending in the applica 4a) Of the above claim(s) <u>7-10</u> is/are withd Claim(s) is/are allowed. Claim(s) <u>1-6</u> is/are rejected. Claim(s) is/are objected to. Claim(s) are subject to restriction and	rawn from con						
Applicati	on Papers							
9)🖾 -	The specification is objected to by the Exar	niner.						
10)⊠ The drawing(s) filed on is/are: a)□ accepted or b)□ objected to by the Examiner.								
	Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).							
	Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).							
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.								
Priority u	nder 35 U.S.C. § 119							
 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). a) All b) Some * c) None of: 1. Certified copies of the priority documents have been received. 2. Certified copies of the priority documents have been received in Application No 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)). * See the attached detailed Office action for a list of the certified copies not received. 								
Attachment	(s)							
	of References Cited (PTO-892)		4) Interview Summary (
3) 🔯 Inform	e of Draftsperson's Patent Drawing Review (PTO-948 nation Disclosure Statement(s) (PTO-1449 or PTO/SE No(s)/Mail Date 01 26 05		Paper No(s)/Mail Date 5) Notice of Informal Page 6) Other: sequence alignment	atent Application (PTO	D-152)			

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Response to Restriction requirement filed Nov. 23, 2005 is acknowledged. Claims 1-10 are pending. Elected claims 1-6, are under examination. Claims 7-10 are withdrawn from the examiner's consideration as directed to non-elected inventions; see 37 CFR 1.142(b).

DETAILED ACTION

1. Election/Restriction

Applicant's election, with traverse, of group I, claims 1-6 in the reply filed on Nov. 23. 2005 is acknowledged. Applicants' traverse is on the ground that restriction between a chemical product and a process for its production is proper when the product can be produced by another method; remarks page 2, third paragraph. argument has been fully considered but is found not persuasive for the reasons given bellow.

The restriction requirement mailed to Applicants on Oct 28, 2005 was as followed:

- "]. Claim 1-6, drawn to a modified sarcosine oxidase, classified in class 435, subclass 189.
- 11. Claim 7-10, drawn to DNA, host cell and recombinant production of the enzyme of group I, classified in class 435, subclass 60.1."

Claims 1-6 are drawn to a modified sarcosine oxidase which is one product.

Claims 7-9 are drawn to another product, i.e. a DNA encoding protein of group I and compositions comprising said DNA. These two products are unrelated because they are not disclosed as capable of use together and they have different modes of Application/Control Number: 10/829,427

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operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In

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the instant case the invention of group I and II are independent chemical entities that

have different structures, biological functions and are not disclosed as capable of use

together. In addition, the search of group I although overlapping is not coextensive with

the search for group II. The search for group II requires searching of class 536,

subclass 23.2; class 345, subclass 320.1 and 435 subclasses 252.3 and 325 as well as

others, which is not necessary for group I.

As to the restriction between group I and claim 10, these inventions are related

as product made and process of making. Such inventions are distinct if either or both of

the following can be shown: (1) that the process as claimed can be used to make other

and materially different product or (2) that the product as claimed can be made by

another and materially different process (MPEP § 806.05(f)). In the instant case the

product, i.e., the enzyme can be produced by a different process, because the enzymes

can be synthesized chemically and not recombinantly.

Furthermore, Applicants are reminded that the US practice requires restriction

between the protein and its encoding DNA, expression vector, host cells and the

recombinant method of production of the protein.

In conclusion, the requirement of restriction is still deemed proper and is

therefore made FINAL.

2. Objections

2.1. Specification and drawings

Description of drawing is unclear. In case of Fig. 1 it is unknown how long and at what temperature the enzyme was incubated at different pH, and what was the time and temperature of activity measurements? In case of Fig. 2 and 3 it is unknown under which pH and at what time the activity was measured. In case of Fig. 4 it is unknown how long and at which pH the enzyme was incubated at the temperatures shown and at which pH and for how long the activity was measured. In case of Fig. 5 it is unknown what was the pH and temperature of the OD measurements. Also, what do letters "m" in the description of y-axis mean?

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors in the specification of which applicant may become aware.

2.2. Claims

The language of the claims is in many places a literary translation from Japanese and does not conform to American practice.

Particularly in claim 5 in points a) to h) colons are not necessary. The examiner suggests the following changes in the language of claim 5:

- 5. A modified sarcosine oxidase wherein said enzyme
- a) hydrolyzes 1 mol of sarcosine to produce 1 mol of glycyne and 1 mol of formaladehyde;
- b) has an optimal pH of about 6.5;
- d) has an optimal temperature of 60° C;

f) retains 90% of activity after 5 hours at pH 6.0 and 25° C and it retains 70% activity after 17 hours at pH 6.0 and 25° C;

- g) has a molecular weight of approximately 43,000daltons (SDS-PAGE), and
- h) has K_m value 5.9 mM at pH 6.5.

Please amend the preamble of claim 6, and add indefinite articles at the beginning of points a)-c) of the claim.

3. Rejections

3.1. 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear in reciting "improved stability in acidic range". For examination purposes it is assumed that the acidic range means "acidic pH range".

Claim 5 is unclear as to the point c) because it is unclear what the term "stable pH range" means. The unclear term renders the claim unclear. For examination purposes it is assumed that the enzyme does not change its activity after being incubated at the range of pH for 5 h at 25° C; see Example 3 page 11.

The claim is also unclear as it is unknown what the term "termostability around 50° C" means. The unclear terms renders the claim unclear. For the examination purposes it is assumed that the enzyme was stable after 10 min heat treatment at 50 mM potassium phosphate buffer and pH 7.5, up to about 50° C.

Claim 6 is unclear in recitation "[a] protein composed of ...", because it is unclear if and of what else said protein is "composed of". The unclear phrase renders the claim unclear. Please use the language which conforms to the U.S. practice, i.e., "consisting of" or "comprising".

2.2. 35 USC section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2.2.1. Written description

Claim 1-4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one

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skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1-4 is generic because it is directed to any modified sarcosine oxidase that has an improved stability in the acidic range of pH. The claim and the dependent claims are lacking a sufficient written description of structure and are completely lacking of written description of improved stability in the acidic range of pH.

Regarding lack of sufficient description of structure, the claims are directed to sarcosine oxidase from any natural source, said oxidase being modified. Applicants teach only one modified sarcosine oxidase, i.e., the enzyme from Bacillus species identified by SEQ ID NO: 1 having the following mutations in comparison with the wild type: Glu61Lys, Asp241Gly and Glu324His. The species identified by SEQ ID NO: 1 is not providing structural identifying characteristics for the whole genus of modified sarcosine oxidases as encompassed by the broad scope of the claims.

Regarding improved stability in the acidic pH range, Applicants teach in Fig. 1 that treatment of the modified enzyme for 5 hours at 25° C at pH 5.5 was deleterious, because in result of it activity decreased to less than 20%. However, the activity at pH of 6 and 6.5 was normal. Applicants do not teach the results for the wild type sarcosine oxidase. Thus, one having skills in the art is not convinced that the modified enzyme has improved stability in the pH of acidic range. Furthermore the term "acidic range" comprises pH from almost 0 to almost 7. Providing data for stability of the modified sarcosine oxidase for only three values of pH, i.e., for 5.5, 6 and 6.5. does not provide

an identifying characteristics of the stability of the enzyme in the whole range of acidic

pH.

Furthermore claim 3 is directed to the modified sarcosine oxidase wherein its

activity in the acidic rangeof pH is improved compared with wild type. Applicants do

not present any comparison of activity of the wild type and modified sarcosine oxidase

in the acidic pH range. Thus claim 3 is completely lacking written description.

In addition claim 4 is directed to a modified sarcosine oxidase wherein K_m value

is less than 6 mM. The claim is generic and lacks sufficient written description of the K_m

values. The specification teaches that the modified enzyme has K_m value of 5.9 at pH

6.5. This, however, does not mean that the Km, under this pH, assumes other values

as well. Furthermore, Applicants do not teach Km values measured for other pH.

In summary, for the reasons explained above as concerns claims 1-4, Applicants

have failed to sufficiently describe the claimed invention in such full, clear, concise and

exact terms that a skilled artisan would recognize Applicants were in possession of the

claimed invention at the time the application was filed.

2.2.2. Scope of enablement

Claim 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the

specification, while being enabling for the modified sarcosine oxidase of SEQ ID NO: 1,

retaining 90% activity after 5 hours treatment at pH 6.0 and 25°C, and retaining 70%

activity after 17 hours treatment under the same conditions, as well as having K_m value

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of 5.9 at pH 6.5, does not reasonably provide enablement for any modified sarcosine

oxidase having

1) improved stability in the acidic pH range,

2) improved activity in the acidic pH range, and

3) K_m value less than 6 mM at pH 6.5.

The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention

commensurate in scope with these claims.

The scope of the claims must bear a reasonable correlation with the scope of

enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue

experimentation is necessary to make the claimed invention. Factors to be considered

in determining whether undue experimentation is required are summarized *In re* Wands

[858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the

nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the

relative skill of those in the art, (e) the predictability of the art, (f) the presence or

absence of working example, (g) the amount of direction or guidance presented, (h) the

quantity of experimentation necessary.

The breath ad nature of the claims encompasses sarcosine oxidase form any

source, modified by men, i.e. all modified sarcosine oxidases, wherein said modified

enzyme has

1) improved stability in the acidic pH range,

2) improved activity in the acidic pH range, and

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3) K_m value less than 6 mM at pH 6.5.

Although the method of modification of DNA molecules so that they encode modified enzymes, their expression and determination of sarcosine oxidase activity are well known in the art and the skills of artisans high, one who would like to make and use the invention is forced to experimentation with a low probability of success absent of teaching the structures of modified sarcosine oxidases. Furthermore the modified sarcosine oxidases have to have

- 1) improved stability in the acidic pH range,
- 2) improved activity in the acidic pH range, and
- 3) K_m value less than 6 mM at pH 6.5.

While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so as to make and use the claimed invention. Specifically, the specification does not provide the exact acidic range, which should be used is such experimentation. Furthermore, the specification is silent as to what stability is considered to be "improved" in comparison with its wild type counterpart. In addition, the specification is silent as to what level of activity is considered to be "improved" in comparison with its wild type counterpart. Moreover, while enablement is not precluded by the necessity for routine screening, in the absence of teaching as to the value of K_m, about which Applicants say only it should be less than 6 mM at pH 6.5, a skilled artisan is forced to

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experimentation that has a low probability of success. There is a continuum of K_m values which are less than 6, and the number of values from 0 to 6 is unlimited.

In addition claim 6 is rejected because the specification, while being enabling for the modified sarcosine oxidase of SEQ ID NO: 1 does not reasonably provide enablement for any modified sarcosine oxidase having 80% identity to SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed as to make and use the claimed invention. Specifically, the specification does not provide any teachings or working example of how to modify SEQ ID NO: 1 so that the sequence after modification were 80% identical to SEQ ID NO: 1 and retained sarcosine oxidase activity. One skilled in the art realizes that a change of even one amino acids in a protein may turned a protein inactive or may change its activity. Thus without teachings as to how to modify SEQ ID NO: 1 so that the protein having 80% identity retains the required activity a skilled artisan is forced to experimentation that has a low probability of success and is, therefore, thus undue.

3.2. 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that

form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a

foreign country or in public use or on sale in this country, more than one year

prior to the date of application for patent in the United States.

Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Nishiya Y. et

al. (Analysis of Interaction between the Arthrobacter Sarcosine Oxidase and the

Coenzyme Flavin Adenine Dinucleotide by Site-Directed Mutagenesis, Applied and

Environmental Microbiology, 1996, 62(7), 2405-2410.

The claim is directed to a modified sarcosine oxidase which is a protein

comprising an amino acid sequence which shows 80% or more homology to SEQ ID

NO: 1 of the instant application. Nishiya Y. et al. disclosed a modified sarcosine

oxidase, obtained by modification of the sarcosine oxidase from Arthrobacter, wherein

said modified sarcosine oxidase is in 85% identical to SEQ ID NO: 1 of the instant

invention application. Nishiya Y. et al. disclosed, therefore the invention claimed by

Applicants.

4. Conclusion

All claims are rejected.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Malgorzata A. Walicka, Ph.D. Art Unit 1652

Patent Examiner

PONNATHAPU ACHUTAMURTHY SUPERVISORY PATERIT EXAMINER

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                                                                                                                                                                                                                                                       MEDLINE=98223334; PubMed=9563845; DOI=10.1007/8004380050685;
Nishlya Y., Toda A., Imanaka T.;
"Gene cluster for creatinine degradation in Arthrobacter sp. TE1826.";
Mol. Gen. Genet. 257:581-586(1998).
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S-Balpha-FAD cysteine (Probable)
G->*! Loss of activity.
A->*D, K: Loss of activity.
A->1,V: Decrease in activity.
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TIGRPAMB; TIGR01377; soxA_mon; 1.
Direct protein sequenting; FAD; Flavoprotein; Oxidoreductase.
INIT_MET 0 37 FAD (ADP part) (Potential).
                  Arthrobacter sp. (strain TE1826).
Bacteria; Actinobacteria; Actinobacteridae; Actinomycetales;
Micrococcineae; Micrococcaceae; Arthrobacter.
NCBL_TaxID=68999;
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"Cloning and sequencing of the sarcosine oxidase
Arthrobacter sp. TE1826.";
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Appl. Environ. Microbiol. 62:2405-2410(1996)
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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     PMVEVPKGIYYGFPSFGGCGLKIGYHTYGQQIDPDTINREFGAYQEDESNLRDFLEKYMP 304
                                                                                                                                                                                                                                                                                                                                                                                                                                             65
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         246 FWVEVPTGIYYGFPSFGGCGLKIGYHTYGQKIDPDTINREFGIYPEDEGNIRKFLETYMP
                                                                                                                                                                                                                                                                                                                                                                                                                                 65 FALRAQELWYELENETHINKI FTKTGVLVFGPKGESDFVAETMEAAAEHSLTVDLLEGDEI
                                                                                                                                                       D->E: Almost no change in activity.
D->N: 100-fold decrease in activity.
C->A.D: Decrease in activity. Stabilizes soxA against chemicals and metal ions.
Stabilizes soxA against chemicals and metal ions.
Stabilizes soxA against chemicals and metal ions.
                                                                                                                                                                                                                                                                                                                                                                                                               5 FDVIVVGAGSMGMAAGYYLAKQGVKTLLVDAFDPPHTEGSHHGDTRIIRHAYGEGRKYVP
                                                                                                                                                                                                                                                                                                                                                                                Gaps
                                                              activity.
of activity; when associated
                of activity.
of activity; when associated
                                                                                                                                                                                                                                                                                                                                                                                 ö
                                                                                                                                                                                                                                                                                                                                                Length 388;
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           Sun G.Q., Ma X.H., Zhou X.L.;
Submitted (MAY-2004) to the EMBL/GenBank/DDBJ databases.
--- CATALYTIC ACTIVITY: Sarcosine + H(2)O + O(2) = glycine
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             Bacillus sp. BSD-8.
Bacteria; Firmicutes; Bacillales; Bacillaceae; Bacillus.
NCBI_TaxID=258797;
                                                                                                                                                                                                                                                                                                                                                                                 36; Indels
                                                                                                                                                                                                                                                                   C->S: Weak activity.

H -> D (in Ref. 2).

D -> A (in Ref. 2).

Wy 61AED62AB11838B6 CRC64;
A->L,W,Y: Weak activity.
                                                                                                                          Weak activity.
Loss of activity.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              Last sequence update)
Last annotation update)
(BC 1.5.3.1).
                                                                                                                                                                                                                                                                                                                                        Query Match
Best Local Similarity 85.1%; Pred. No. 2.6e-119; Matches 326; Conservative 21; Mismatches 76.
                                                                                                         M->G: Weak activity.
G->A: Weak activity.
D->A: Loss of activi
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   387 AA
                  Loss
                                                              S->P: Weak
M->G: Loss
with P-15.
                                                                Weak
                                                                             Loss
                G->A: LOSS
S->P: LOSS
with G-16.
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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  Created)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        GKTEHDISIFSINRPALKQKTTI
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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 05-JUL-2004 (TrEMBLrel. 27, 05-JUL-2004 (TrEMBLrel. 27, 05-JUL-2004 (TrEMBLrel. 27,
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                Monomeric sarcosine oxidase
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   C6_9BACI
Q6ITC6_9BACI PRELIMINARY;
Q6ITC6;
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17
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   114
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                                                                                                                                                                                                                                                                                                                    388 AA;
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17
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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    Name=sox;
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                                                                                                                                                                                                                                                                    MUTAGEN
CONFLICT
CONFLICT
SEQUENCE
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                                                                                                                                                         MUTAGEN
MUTAGEN
MUTAGEN
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